CHAPTER 11

MYOSIN VII

AZIZ EL-AMRAOUI, AMEL BAHLOUL AND CHRISTINE PETIT

Unité de Génétique des Déficits Sensoriels, INSERM UMRS 587, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris cedex 15, FRANCE

Abstract: Class VII myosins are among the most widely expressed myosins in the animal kingdom. They also have a broad tissue expression. Vertebrates and some invertebrates possess two different myosins VII, myosin VIIa and myosin VIIb, which may differ in their kinetic properties. Defects in myosin VIIa cause phenotypic anomalies in *Drosophila*, zebrafish, mouse and humans. In humans, loss-of-function mutations in the myosin VIIa gene cause Usher syndrome type I, a dual sensory defect that combines sensorineural deafness and retinitis pigmentosa leading to blindness. Some progress has been made in the characterization of the enzymatic properties of the myosin VII head domain, leading to the view that myosin VIIa may both exert tension at given subcellular emplacements, and move cargos (molecules or organelles) along actin filaments. The formation of myosin VII dimers *in vivo*, however, remains to be shown. Based on the analysis of mutant phenotypes and the deciphering of myosin VIIa-associated molecular networks, some of the roles played by myosin VIIa in the developing inner ear and the retina have been elucidated. In the inner ear sensory cells, myosin VIIa probably acts as a conveyer of several Usher syndrome proteins that are involved in the differentiation of the hair bundle, the structure receptive to sound or acceleration. In the retina, myosin VIIa transports melanosomes and phagosomes in pigment epithelium cells, and opsins in photoreceptor cells.

Keywords: myosin VIIa, Usher I syndrome, shaker-1, hair bundle, protein trafficking, melanosomes

11.1. THE CLASS VII MYOSINS: STRUCTURAL FEATURES AND PHYLOGENIC GROUPING

Class VII myosins evolved after the offshoot of plants, but before the divergence between fungi and metazoans (Thompson and Langford, 2002; Richards and Cavalier-Smith, 2005; Foth et al., 2006). Their presence has been reported in various animals, including slime molds, worms, flies, fish, frogs, and humans. At first, a myosin VII fragment was identified in *Drosophila*, using a PCR strategy designed to uncover new unconventional myosins (Cheney et al., 1993). Shortly

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after, myosins VII started to be characterized in vertebrates too. In particular, murine (2215 amino acids, accession number AAB40708) and human (2215 amino acids, accession number AAB03679) myosin VIIa full-length sequences were reported when mutations in the corresponding genes were found to cause deafness both in humans (Weil et al., 1995, 1996; Chen et al., 1996) and mice (Gibson et al., 1995; Mburu et al., 1997). Vertebrates and some invertebrates synthesize two class VII myosins, known as myosin VIIa and myosin VIIb, from two different genes. In humans, the *MYO7A* and *MYO7B* genes have 48 and 45 coding exons, and span approximately 87 kb and 102 kb of genomic sequence at chromosome 11q13.5 and 2q14.3, respectively (Weil et al., 1996; Chen et al., 2001; http://genome.ucsc.edu).

All class VII myosins are composed of a motor head domain that harbors both ATP and actin binding sites, a neck region composed of four or five IQ (isoleucine-glutamine) motifs (Figure 11.1A, B), and a long tail region (1359 amino acids in HsMyosin VIIa) with several domains (Kiehart et al., 2004; Richards and Cavalier-Smith, 2005; Foth et al., 2006). These are a predicted coiled-coil domain (absent in vertebrate myosins VIIb and *C. elegans* myosin VII), followed by two large repeats of ~460 amino acids, each containing a myosin tail homology 4 (MyTH4) and a band 4.1, ezrin, radixin, moesin (FERM) domain, separated by an SH3 domain (see Figure 11.1A). In addition, homology modeling of the *Drosophila* myosin VIIa head sequence has revealed an N-terminal SH3-like subdomain (~56 amino acids), comparable to that seen in myosins II. This previously overlooked domain is present at the N-terminal end of all the vertebrate and invertebrate myosins VII identified so far (Kiehart et al., 2004). Analysis of the crystal structures of the FERM domains from ezrin, radixin and moesin has shown that these domains consist of three ~100 amino acid-subdomains or lobes (Pearson et al., 2000; Kiehart et al., 2004, and references therein). Kiehart and colleagues have pointed out that only the first two

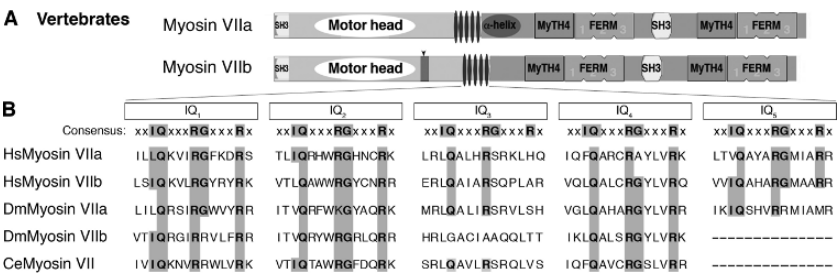

Figure 11.1. (A) The vertebrate myosin VII head and neck are characterized by an N-terminal SH3-like subdomain, a typical motor domain followed by five IQ (isoleucine-glutamine) motifs that bind calmodulin. The long tail starts with an α-helical domain in myosin VIIa but not myosin VIIb, followed by two large repeats, each containing a *my*osin *t*ail homology 4 (MyTH4), and a band *4*.1, *E*zrin, *R*adixin, *M*oesin (FERM)-like domain, separated by a src homology 3 (SH3) domain. Myosin VIIb displays an insertion in the motor domain (arrowhead). (B) Sequence comparison of the neck region in myosins VII. Residues in bold indicate similarity to the consensus sequence shown above the alignment. The conserved positions are shaded. Abbreviations: Hs, *Homo sapiens;* Dm, *Drosophila melanogaster*; Ce, *Caenorhabditis elegans*